P980022

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUN 15 1999

Re: P980022
MiniMed Continuous Glucose Monitoring System
Filed: December 17, 1997
Amended: August 20 and November 3, 1998; January 28, February 10, March 16, March 17, April 7, May 10, and May 28, 1999

Dear Mr. Faillace:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the MiniMed Continuous Glucose Monitoring System. This device is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace blood glucose information obtained using standard home glucose monitoring devices. The information collected by CGMS may be downloaded and displayed on a computer and reviewed by healthcare professionals. This information may allow identification of patterns of glucose level excursions above or below the desired range, facilitating therapy adjustments, which may minimize these excursions.

- The system is intended for prescription use only,
- Will not allow readings to be made available directly to patients in real time,
- Provides readings that will be available for review by physicians only after the entire recording interval (suggested as 72 hours),
- Is currently intended for occasional rather than everyday use, is to be used only as a supplement to, and not a replacement for, standard invasive measurement,
- Is not intended to change patient management based on the numbers generated, but to guide future management of the patient based on response to trends noticed. That is, these trends or patterns may be used to suggest when to take fingerstick glucose measurements to better manage the patient.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter. The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

[redacted]e printed material issued
[redacted]espect to this device
[redacted] for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

[redacted]TION (PMA) SUPPLEMENT. Before making any change [redacted]veness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supple[redacted]ust be submitted if the device is to be modified and the modified [redacted]d be subjected to animal or laboratory or clinical testin[redacted]mine if the modified device remains safe and eff[redacted]

A [redacted]Being Effected" is limited to the labe[redacted]ring process changes specified under 21 CFR 81[redacted]on of, but not the replacement of previousl[redacted]cifications and test methods. These changes may [redacted] approval upon acknowledgment by FDA that the submission [redacted]as a "Special PMA Supplement - Changes Being Effected." This [redacted] is in addition to that issued by the PMA Document Mail Cente[redacted] PMA supplements submitted. This procedure is not applicable to changes [redacted] device design, composition, specifications, circuitry, software or energy source.

be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

ny significant chemical, physical or other change or deterioration he device or any failure of the device to meet the specifications blished in the approved PMA that could not cause or contribute to h or serious injury but are not correctable by adjustments or other tenance procedures described in the approved labeling. The report l include a discussion of the applicant's assessmer of the change, or failure and any proposed or implemente rective nt. When such events are correct ed adjustments or other maintenance procedures described ed labeling, all such events known to the applicant shall d in the Annual Report described under "Postapproval Report nless specified otherwise in the conditions of approval to this This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

(1)may have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Th ame events subject to reporting under the MDR Regulatio may also be s to the above "Adverse Reaction and Device Defect Re ng" r in the "Conditions of Approval" for this PMA. s determined t cative reporting is unnecessary. Whenever ar nvolving a d ct to reporting under both the MDR Regulation " Approval" for a PMA, the manufacturer shall s a eports required by the MDR Regulation within the as 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

ritten report is to be submitted to:

nd Drug Administration
r Devices and Radiological Health
e Reporting

20847-3002

336&1336)and FDA publications entitled "An
ing Regulation" (FOD # 509) and "Medical
#987) are available on the CDRH WWW
CDRH's Fact-On-Demand (F-O-D) at
can be made by sending a
Assistance (DSMA) at 301-

III. DEVICE DESCRIPTION

A. Overview

The MiniMed Continuous Glucose Monitoring System (CGMS) is comprised of five principal components: (1) a monitor, (2) a sterile, disposable subcutaneous glucose sensor with an external electrical connector, (3) a connecting cable, (4) a Com-Station which allows data stored in the monitor to be downloaded to a personal computer, and (5) a test plug used to confirm the function of the sensor, cable and monitor. The system is designed to provide continuous measurement of glucose concentration in interstitial fluids over a range of 40 to 400 mg/dL. The information collected by the CGMS is intended to provide adjunctive data to physicians who are interested in monitoring the daily fluctuations in their subjects' glucose levels.

B. Description of Components

Glucose Monitor:

The glucose monitor, approximately the size of a pager, serves as a data collection unit which processes the signal received from the glucose sensor.

The glucose monitor is designed to provide power to the sensor, measure the sensor current, perform data smoothing and filtering, facilitate device calibration, provide storage of historical glucose data and transfer data to a personal computer via an infrared serial communication port.

The glucose sensor signal is acquired every 10 seconds. A smoothed average of acquired signals is saved in memory every 5 minutes.

The monitor is capable of storing glucose signals for up to 14 days. The glucose sensor signal acquisition occurs continuously once the CGM is turned on and initialized.

The display of the glucose monitor is a LCD utilizing a combination of fixed icons, seven-segment numeric characters and sixteen-segment alphanumeric characters. Backlighting can be activated with a single button push.

The user enters configuration, control, and calibration information via five membrane keypad buttons; SEL, ACT, ↑, ↓, and ON/OFF. Using a variety of combinations of information displayed on the LCD screen and the keystrokes made by the user, the CGM is configured to perform its built-in functions and indicate the status related to them. The screens and the keystrokes are organized according to a well-defined menu structure. Visual (alarm and alert displays) and audible (alert tones and tone sequences) indications are provided to alert the user of error conditions.

Glucose Sensor:

The Glucose Sensor consists of glucose sensing electrodes plated on a flexible substrate housed in a polyurethane tube; a rigid introducer needle; a base disk containing contact pads which act as electrical connectors; a seal which provides a water tight connection; a needle guard; and an adhesive patch.

The components are assembled and sealed in a pouch with sterilization and temperature indicators. The Glucose Sensor is a sterile disposable unit. The customer box includes an additional temperature indicator.

Cable:

The cable provides a continuous link between the glucose sensor and the glucose monitor. It consists of a grounded, coated copper cable; a male, four-pin connector plug to the monitor; and a female, three leaf spring connector to the glucose sensor.

Com-Station:

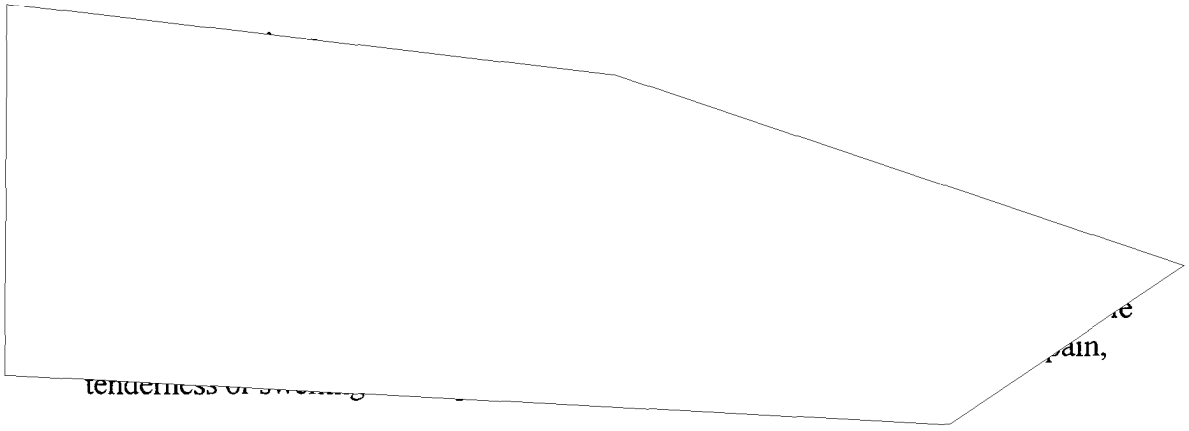
The Com-Station is a cradle-like unit that is form-fit for the monitor. The Com-Station converts infrared (IR) pulses from the monitor into RS-232 compatible electrical pulses that are sent through a serial port to the PC. A second RS-232 serial port allows the Com-Station to act as a pass through connection to allow the user to connect any serially accessed peripheral device to their PC without disconnecting the Com-Station. A compatible glucose meter may be connected to the PC utilizing the pass-through feature. The Com-Station allows retrieval and review of the patient's glucose monitor data.

A switch selects between IR communication and the second RS-232 connector. An AC adapter powers the unit. An illuminated ON/OFF switch indicates to the user when power is applied.

Windows 95 compatible PC Resident software (model 7310) is provided with the Com-Station. This software retrieves data from the monitor, performs error checking to ensure data integrity, and produces an output file in text format, which may be reviewed using Excel™. Macros are provided to facilitate the generation of several standard report formats.

Test Plug:

The test plug is a device that can simulate a sensor, or a cable and sensor, in order to provide the user with system diagnostic data. The test plug, when connected to the cable in place of a sensor, sends a constant electric signal to the monitor. If the monitor reads the electric signal, then the monitor and cable are functioning properly. Likewise, the test plug can be inserted directly into the monitor to deliver the constant current, and determine if the monitor is functional.



- The CGMS does not display glucose values and is intended to be used in addition to, not in place of, home glucose monitoring performed using a standard home glucose meter. During use of the CGMS, diabetes treatment should continue to be based on standard, periodic finger stick blood glucose measurements.

- Successful use of the CGMS requires some visual and auditory acuity. Use of the CGMS is not recommended for patients whose impaired vision or hearing does not allow full recognition of the monitor signals and alarms.

E. Precautions

- CGMS users should be trained to insert and replace Glucose Sensors, to program and operate the Glucose Monitor, and to respond to alarm conditions prior to attempted use of the system.

- Always wash hands with soap and water before opening the Glucose Sensor package. After opening the package, avoid touching any Glucose Sensor surfaces that will come in contact with the body (i.e., sensor, needle, connector adhesive surfaces and bandage).

- Before inserting the sensor, always clean the skin at the sensor insertion location with a topical antimicrobial solution, such as isopropyl alcohol.

- After sensor insertion, check the insertion location often for redness, bleeding, pain, tenderness and swelling, especially before going to bed in the evening and after waking up in the morning.

- Establish a rotation schedule for choosing each new sensor location. Avoid sensor locations that are constrained by clothing, accessories or subjected to rigorous movement during exercise.

- Monitors should be placed in ShowerPaks, prior to taking a shower or engaging in other activities in which the monitor would be expected to get wet. Do not submerge the monitor.

- Contact sports or other activities which may damage the monitor should be avoided. Prior to exercising, CGMS users should make sure that the sensor connector and monitor are securely fastened to their bodies.

- If the Glucose Sensor is disconnected and then reconnected again, the signals it sends to the monitor may not be stable or accurate. The sensor may need to be recalibrated and reinitialized before returning to normal operation.

- Users who also wear an insulin pump should make sure that the sensor insertion site is at least 3 inches from the insulin infusion site. Users who inject insulin should administer injections at least 3 inches away from the sensor insertion site.

- The Glucose Sensor is sterile in its unopened, undamaged package. Do not use any Glucose Sensor if its sterile package has been previously opened or damaged.

- The current and voltage signals shown in the monitor are to be used only for finding potential problems with the CGMS and do not directly indicate the current glucose value.

- If the monitor shows a "NO POWER" alarm for more than two (2) hours, the glucose data and program information in the memory will be lost. If this occurs, all program information will return to the manufacturer's default settings after the batteries are replaced. Users must first reprogram the monitor and then reinitialize and calibrate the sensor before returning to normal operation.

- Using the monitor in close proximity to strong electromagnetic sources such as medical imaging equipment, television and radio transmitters and high voltage power lines is not recommended.

IV. USE IN SPECIAL PATIENT GROUPS

The monitor has been clinically tested primarily in adult Caucasian persons with Type I diabetes. This device has not been tested in children. Because of variations in size and the amount of body fat, performance may be different in children relative to that observed when the device is used in adults. Although the system has not been studied in other diabetic patient populations, similar results are expected.

Use of the monitor may not be applicable for patients who are not motivated to operate it, are physically unable to operate it, have unrealistic expectations about its value and do not have a good support system at home for responding to alarms.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Periodic self-glucose monitoring using home glucose meters will provide information regarding variations in glucose levels, although not on a continuous basis.

VI. MARKETING HISTORY

The CGMS has not been marketed in any country.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Insertion of a Glucose Sensor into the skin may result in infection, inflammation or bleeding at the Glucose Sensor insertion site.

VIII. SUMMARY OF STUDIES

A. Laboratory Studies

1. Microbiological

(a) Sterility Assurance

The electron beam (EB) sterilization process used to sterilize the sensor assembly was validated according to the requirements of ISO 11137 Method 1.[1] A theoretical device bioburden of 19.7 colony forming units (CFUs) was calculated based on testing performed on ten devices from three different production lots. Based on these results, a total of 100 sensor assemblies were exposed to a sublethal dose of 6 kGy. All samples tested negative for surviving organisms following sterilization. These results indicate that the selected sterilization dose of 18.7 kGy will provide a sterility assurance level of 10^{-6}.

(b) Pyrogenicity

Pyrogenicity was assessed in rabbits using a USP XXII Pyrogen Assay.[2] Extracts were obtained from complete sensor assemblies. All testing performed indicated that the sensor assembly is non-pyrogenic.

2. Biocompatibility Testing

Several *in vitro* and *in vivo* tests were performed on glucose sensors and the polyurethane tubing which houses the sensor during implantation to determine the level of risk associated with the subcutaneous insertion of this device. Testing was based on the FDA's Tripartite Biocompatibility Guidance recommendations for a short-term tissue-contacting device.[3] The results of these tests are listed in Table 1:

Table 1: Biocompatibility Test

Test	Sensor	Tubing	Result
[redacted]		x	non-reactive
		x	non-hemolytic
Mutagenicity (Ames test, saline extract)	x	*	non-mutagenic
Cytotoxicity (MEM elution, L-929 cells)	x	x	non-cytotoxic
Guinea Pig Maximization (saline, cottonseed oil)	x	x	weak sensitizer (Class I)
Subacute Toxicity (14 day intravenous dosing study in mice)	x	*	non-toxic
USP Acute Systemic Toxicity (saline, cottonseed oil)	x	x	non-toxic
[redacted]			no significant reaction
USP Muscle Implantation (30 day)	x	*	no significant reaction

* Mutagenicity, subacute toxicity, and 30-day USP muscle implantation testing was not conducted on the tubing since ISO-10993 states that these tests are not required for [redacted] short-term tissue contact.

3. Accuracy and Precision

Sensors were studied *in vitro* for accuracy and precision after calibration by placing the sensors in solutions with known glucose concentrations. These control solutions were quantified using a [redacted] glucose analyzer (Yellow Springs Inc., Yellow Springs, Ohio) and a linear calibration curve was constructed [redacted] 250 mg/dL and 350 mg/dL glucose). Accuracy and precision were determined by comparing calculated sensor glucose concentration to that of the YSI measured glucose concentration via a percent error calculation. The average percent error was determined for twelve sensors from three different manufacturing lots. The average error at each glucose concentration was also determined.

[redacted] ge percent error between the YSI determined concentration and the sensor [redacted] ed concentration was 11.9%. A comparison of YSI glucose versus sensor calculated glucose values revealed an average correlation coefficient of [redacted] average y-intercept of [redacted] and an average slope of 0.96. The coefficient of variation was less than [redacted] sensors tested.

4. Stability

[redacted] ng sensors in a 100 [redacted] r drifted less than

5. Interferences

Sensor response to ascorbic acid, acetaminophen, uric acid and oxygen was evaluated by placing sensors in phosphate buffered saline (PBS) solutions containing physiologically relevant concentrations of the potentially interfering substance. The sensor output current was monitored and compared to the output currents of the same sensor equilibrated in PBS. These studies indicated that there was no significant change in sensor output associated with exposure to these potentially interfering substances.

6. Electromagnetic Compatibility

Monitors were connected to test loads and tested for both electromagnetic emissions and immunity in accordance with the following test standards:

MIL-461/462D (magnetic emissions and magnetic immunity)[4]
EN 55011 (radiated emissions)[5]
IEC 61000-4-3 (radiated immunity)[6]

All devices met the requirements of these standards, confirming that the CGMS will not be adversely affected by normally encountered electronic equipment nor will the CGMS interfere with electronic equipment in close proximity to the device. During testing at levels higher than those specified in the standards, it was noted that incorrect signal values were displayed by the monitor when exposed to high intensity fields. As a result of this finding, the Instructions For Use for the CGMS was revised to state that the device should not be used in close proximity to sources of high intensity electromagnetic fields such as high power radio or television transmitters or high voltage power lines.

7. Electrostatic Discharge

Six functional monitors were subjected to electrostatic discharge testing according to the requirements of IEC 61000-4-2.[7] Contact (2, 4, 6 and 8 kV) discharges were applied to multiple points on the monitor. All test samples passed functional testing performed following exposure to these discharges.

8. Environmental Testing (Monitor)

(a) Mechanical Vibration

Six monitors were subjected to mechanical vibration testing using a random vibration profile for 10 minutes at 6.3 g RMS. Functional testing performed after vibration exposure confirmed that no units were damaged by this testing.

(b) Mechanical Drop

Six monitors were dropped from a height of 36 inches onto a linoleum covered concrete floor onto each of the device's six surfaces. All samples passed functional testing performed after the drops.